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Maternal exposure to childhood abuse is associated with elevated risk of autism

Andrea L. Roberts, PhD[*,1], **Kristen Lyall, ScD**[2,3], **Janet W. Rich-Edwards, ScD**[4], **Alberto Ascherio, DrPH**[2,5,6], and **Marc G. Weisskopf, PhD, ScD**[5,6]

[1]Department of Society, Human Development and Health, Harvard School of Public Health

[2]Department of Nutrition, Harvard School of Public Health

[3]University of California Davis, MIND Institute

[4]Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital

[5]Department of Epidemiology, Harvard School of Public Health

[6]Department of Environmental Health, Harvard School of Public Health

Abstract

Context—Adverse perinatal circumstances have been associated with increased risk of autism. Women exposed to childhood abuse experience more adverse perinatal circumstances than women unexposed, but whether abuse is associated with autism in offspring is unknown.

Objective—To determine whether maternal exposure to childhood abuse is associated with risk of autism, and whether possible increased risk is accounted for by higher prevalence of adverse perinatal circumstances among abused women, including gestational diabetes, preeclampsia, selective serotonin reuptake inhibitor use, intimate partner abuse, prior abortion, pregnancy less than 37 weeks, low birth weight, alcohol use, and smoking during pregnancy.

Design and Setting—Nurses' Health Study II, a population-based longitudinal cohort of 116,430 women.

Patients or Other Participants—Participants with data on childhood abuse and child's autism status (97% White). Controls were randomly selected from among children of women who did not report autism in offspring (N mothers of children with autism = 451; N mothers of children without autism=52,498).

Main Outcome Measure—Autism spectrum disorder, assessed by maternal report, validated with the Autism Diagnostic Interview-Revised in a subsample.

Results—Exposure to abuse was associated with increased risk of autism in children in a monotonically increasing fashion. The highest level of abuse was associated with the greatest

[*]Corresponding author address: Department of Epidemiology, Kresge Building, Harvard School of Public Health, 677 Huntington Avenue, Boston MA 02115. aroberts@hsph.harvard.edu. Tel: 617-416-8155. Fax: 617-566-7805.

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prevalence of autism (1.8% versus 0.7% in women not abused, P = 0.005) and the greatest risk for autism adjusted for demographic factors (risk ratio=3.7, 95% confidence interval=2.3, 5.8). All adverse perinatal circumstances were more prevalent in women abused except low birth weight. Adjusted for perinatal factors, the association of maternal abuse with autism was slightly attenuated (highest level of abuse, risk ratio = 3.0, 95% confidence interval=1.9, 4.9).

Conclusions—We identify an intergenerational association between childhood exposure to abuse and risk for autism in the subsequent generation. Adverse perinatal circumstances accounted for only a small portion of this increased risk.

Keywords

Autism; childhood abuse; birth weight; smoking; intimate partner abuse; prenatal factors

Introduction

Although the etiology of autism is mostly unknown, many hypotheses focus on the perinatal period as potentially critical for the development of autism. Prematurity[1], low birth weight[1,2], gestational diabetes, hypertension[3], prolonged[1] or very short labor[4], maternal uterine bleeding[5], being small for gestational age[6], and gestation less than 35 weeks[7] have been associated with elevated risk of autism. Additionally, maternal smoking,[6] use of selective serotonin reuptake inhibitors,[8] and exposure to intimate partner violence in the prenatal period[9] have been associated with higher risk of having a child with autism. Before and during pregnancy, women exposed to childhood abuse are more likely than those unexposed to experience circumstances and engage in behaviors that may be detrimental to the fetus, including smoking[10,11], drug use[11–14], overweight[15,16], stress[11,17] and intimate partner violence victimization[18–20]. Experience of childhood abuse is also associated with unintended pregnancy[21], preterm labor[22] and low birth weight[11]. Thus, maternal exposure to childhood abuse may be a risk factor for autism. Yet, to our knowledge, the association between maternal exposure to childhood abuse and risk of autism has not been examined.

In this paper we assess the relationship between maternal exposure to childhood abuse and risk of autism in a large population-based cohort. We further examine several perinatal exposures as possible mediators of the potentially elevated risk of autism in children of women exposed to childhood abuse.

Methods

Sample

We use data from the Nurses' Health Study II (NHSII), a cohort of 116,430 female nurses originally recruited in 1989 from 14 populous U.S. states and followed up with biennial questionnaires. We examine data from women who reported whether they had ever had a child with autism spectrum disorder and who answered a supplemental 2001 questionnaire about childhood abuse (n=54,963 women). The Partners Healthcare Institutional Review Board approved this research. Completion and return of questionnaires sent by U.S. mail constitutes implied consent.

Measures

Selection of cases and controls—In the 2005 biennial questionnaire, we asked respondents if they had a child diagnosed with autism, Asperger's syndrome, or other autism spectrum disorder. In 2007–2008 we sent a follow-up questionnaire to 756 women currently participating in NHS II who responded that they had a child with any of these diagnoses, querying the affected child's sex, birth date, and diagnoses (response rate=84%, n=636).

Some cases were excluded based on responses to the follow-up questionnaire. If women reported any of the following overlapping circumstances, they were excluded: they did not have a child with autism (n=32); the affected child was adopted (n=9); they did not want to participate (n=20); or they did not report the child's birth year (n=71). Women who reported the affected child had trisomy 18, Fragile X, an XXY genotype, or Down, Angelman, Jacobsen's, or Rett's syndrome were also excluded (n=11). Here we refer to 'cases' as children meeting these inclusion criteria; we use 'autism' to refer to autism spectrum disorder. Of the remaining 549 cases, 98 women did not participate in the questionnaire assessing childhood abuse, leaving 451 cases. Women who reported they had a child with autism in the 2005 questionnaire but were not included in the analyses (N=389) were similar to women who reported a child with autism and were included in analyses (N=451) on year of birth (median = 1957 for both groups), marital status (83.0% of women not included were married versus 85.8% of included women), and smoking status at NHSII enrollment in 1989 (10.3% of excluded women were smokers versus 11.0% of included women).

Autism diagnosis was validated in a subsample of cases by telephone interview of 50 randomly selected mothers who indicated willingness to complete the interview (81% of mothers were willing to be interviewed), using the Autism Diagnostic Interview-Revised (ADI-R)[23,24]. Women who agreed to participate in the validation substudy were similar in the ASD diagnoses reported in their child to women who were not willing to participate (women willing to participate: 25% reported autism, 51% Asperger's, and 25% pervasive developmental disorder – not otherwise specified (PDD-NOS); women not willing to participate: 25% reported autism, 49% Asperger's, and 23% PDD-NOS). Women not willing to participate in the validation study also did not differ from those willing to participant on child's year of birth, sex, low birth weight prevalence or prematurity status.

In this substudy, 43 children (86%, 95% confidence interval=74%, 93%) met ADI-R criteria for an autism diagnosis, defined by meeting cutoff scores in all 3 domains and having onset by age 3 years; the remaining individuals met the onset criterion and communication domain cutoff, and either missed full diagnosis by one point in one domain (n=5) or met cutoffs in one or two domains only (n=2). The ADI-R provides an algorithm for full autistic disorder but not autism spectrum disorder. It is important to note that all children in the validation study demonstrated autistic behaviors. Children who did not meet full ADI-R criteria narrowly missed, thus may be on the autism spectrum.

Controls were parous women who reported never having a child with autism and who responded to the 2001 questionnaire reporting year and sex of each birth and childhood abuse. To assure independence of maternal characteristics among controls, we randomly selected one birth per woman with data on childhood abuse from among her live births (n=

52,498). At baseline in 1989, women included in our analyses were more likely to have ever been pregnant (91% versus 68%), less likely to smoke (29% versus 36%), and more likely to be White (97% versus 94%) compared with women not included.

Maternal exposure to childhood abuse: Abuse experiences were assessed in 2001. Combined childhood physical and emotional abuse before age 12 years was assessed with 5 questions from the Physical and Emotional Abuse Subscale of the Childhood Trauma Questionnaire[25] querying the frequency of people in the family: 1) hitting so hard it left bruises, 2) punishing in a way that seemed cruel, 3) insulting, 4) screaming and yelling, and 5) punishing with a belt or other hard object. For each item, response options included never, rarely, sometimes, often, or very often true. Responses were assigned values from 0 (never) to 4 (very often) and were summed following questionnaire scoring recommendations. In a validation study, the scale had good internal consistency (Chronbach's α=0.94) and test-retest reliability (intraclass correlation = 0.82) over a 2- to 6-month interval[25]. The resulting scale was divided approximately into quartiles to calculate risk ratios and to investigate a possible dose-response relationship between severity of child abuse and risk of autism.

Sexual abuse occurring in two time periods was assessed, before age 12 years and age 12 to 17 years. For each time period, two questions queried unwanted sexual touching by an adult or older child and forced or coerced sexual contact by an adult or older child[26]. Response options included never, once, or more than once. To create a single measure, we assigned one point for each "once" answer and two points for each "more than once" answer. We then grouped these points for analysis as follows: 0 points was considered no abuse, 1 or 2 points was considered "mild" abuse, 3 or 4 points was considered "moderate" abuse, and 5 or more points was considered "severe" sexual abuse.

As exposure to high levels of both sexual and physical and emotional abuse could be associated with greater risk of autism in offspring than exposure to either type alone, we also created a measure of combined physical, emotional and sexual abuse by summing the physical/emotional and sexual abuse measures.

Potential mediators: In 2001, birth weight, smoking and alcohol use during pregnancy, and lifetime exposure to intimate-partner emotional, physical and sexual abuse was assessed. Birth weight was by maternal report in five categories: below 5, 5 to 5.4, 5.5 to 6.9, 7.0 to 8.4, 8.5 to 9, and above 9 pounds. Smoking during pregnancy was assessed with a single question: "how many cigarettes did you smoke per day during this pregnancy?" Responses were dichotomized as any/none. Alcohol use during pregnancy was assessed with the question: "on average, how much alcohol did you drink per week during this pregnancy?" As very few women had more than 1 drink/week, response options were coded as none, 1, or 2 or more drinks/week.[27] Lifetime history of intimate partner abuse was assessed in 2001 with a modified version of the Assessing Abuse Scale[28]. Fear of partner and emotional, physical, and sexual abuse were each assessed with one question: "Have you ever been made to feel afraid of your spouse/significant other?" (fear of partner); "Have you ever been emotionally abused by your spouse/significant other?" (emotional abuse); "Have you ever been hit, slapped, kicked or otherwise physically hurt by your spouse/significant other?"

(physical abuse); “Has your spouse/significant other ever forced you into sexual activities?” (sexual abuse). Following these questions, respondents indicated the calendar years in which any of the types of abuse occurred. We included abuse in the year before the birth year as a potential mediator as abuse in the calendar year before the birth year has been associated with risk of autism.[9] Having had an abortion prior to the birth of the index child was coded dichotomously based on lifetime history of abortions, including ages at occurrences, assessed in 1993 and updated in 1997, 1999, and 2001. Gestational diabetes was coded dichotomously from questions regarding history of gestational diabetes and year of diagnosis, assessed retrospectively in 1989 and updated biennially. Lifetime history and age at occurrences of toxemia/preeclampsia during pregnancy, defined for the respondent as “raised blood pressure and proteinuria” was assessed in 1989 and updated biennially.

Selective serotonin reuptake inhibitor use was assessed biennially from 1996 to 2007[8,29]. Women were asked whether in the past two years they had regularly used Paxil, Prozac, or Zoloft. Women using any of these were coded as having used a selective serotonin reuptake inhibitor (SSRI) in the perinatal period for births occurring in the two years queried by the questionnaire. As the first SSRI (Prozac) was available in the US in 1988[30], all women who gave birth prior to 1988 were coded as not having used an SSRI during pregnancy. Additionally, women were asked in 1993 whether they had ever used Prozac or Zoloft. Women who reported never having used these were coded as not having used SSRIs during births in 1993 or earlier. Women who reported that they had ever used an SSRI and whose child was born between 1989 to 1993 were excluded from analyses using this variable. Although these women had used an SSRI sometime during the 4-year time period queried, it is unknown whether they used an SSRI during the pregnancy that occurred during these years. Maternal age at child’s birth was coded as: less than 25, 25 to 29, 30 to 34, 35 to 39, and 40 years or older. Year of child’s birth was continuous, and maternal childhood socioeconomic status was measured by the maximum of her parents’ education in her infancy.

Analyses

We first ascertained whether maternal physical/emotional, sexual, and combined abuse were associated with risk of autism in children using χ^2 tests. We next examined the prevalence of perinatal risk factors by maternal childhood abuse status. To determine whether maternal childhood abuse was associated with risk of autism in children after adjusting for potential confounders, we modeled autism risk with either maternal childhood physical/emotional abuse, sexual abuse, or combined sexual, physical, and emotional abuse adjusted for maternal childhood socioeconomic status, maternal age at birth, birth year, and child’s sex.

To examine potential mediation by perinatal risk factors, we modeled autism risk as a function of combined maternal sexual, physical, and emotional abuse, perinatal risk factors and potential confounders. We assessed mediation proportion using the SAS Mediate macro[31,32]. Finally, we conducted models stratified by child’s sex to investigate possible sex-specific relationships between maternal childhood abuse and autism risk.

We used generalized estimating equations with a log link and Poisson distribution to estimate risk ratios[33]. To calculate statistical significance for the prevalence of gestational

risk factors by combined childhood physical, emotional and sexual abuse, we modeled each risk factor as a dichotomous dependent variable with childhood abuse as the independent variable using generalized estimating equations with a log link and binomial distribution. To calculate statistical significance for the prevalence of alcohol use, which was measured in three levels, we used ordered logistic regression with a cumulative logit link and a multinomial distribution.

Results

Approximately 3% of women (n = 1788, 3.4%) were exposed to serious sexual abuse. Prevalence of autism was elevated but not statistically significantly in children of women exposed to serious sexual abuse compared with children of women unexposed to sexual abuse (1.3% of children of women exposed were autistic versus 0.8% of children of women unexposed, $P = 0.11$). Women exposed to physical and emotional abuse were more likely to have a child with autism (highest quartile abuse, 1.1% of children were autistic; no abuse, 0.7% of children were autistic, $P = 0.003$). The highest level of mother's combined sexual, physical, and emotional abuse was associated with the greatest prevalence of autism in children (1.8% of children versus 0.7% of children of women not abused, $P = 0.005$).

Mother's combined childhood physical, emotional and sexual abuse was associated with increased prevalence of nearly all adverse circumstances in the perinatal period, in dose-response fashion (Figure). Women exposed to the highest level of abuse, compared with women not exposed to abuse, were more likely to smoke during pregnancy (17.4% versus 8.8%), drink alcohol (5.1% versus 2.8% had more than 1 drink/week), have gestational diabetes (5.3% versus 2.7%), preeclampsia (7.7% versus 3.6%), a prior abortion (15.9% versus 10.0%), gestation of less than 37 weeks (9.4% versus 7.1%), use selective serotonin reuptake inhibitors in the perinatal period (0.4%, versus 0.2%), and be victimized by intimate partner abuse in the year before the birth year (23.3% versus 6.1%). Women exposed to childhood abuse were not statistically significantly more likely to give birth to a child who weighed less than 5 pounds; however, they were more likely to have a child who did not weigh 7 to 8.5 lbs, the birth weight range that has been associated with lowest infant mortality[34].

In models adjusted for demographic variables (but not perinatal risk factors), women exposed to either sexual or physical/emotional abuse were more likely to have a child with autism in a monotonically increasing fashion (Table 1, Models 1 and 2). Combined sexual, physical and emotional abuse was also associated with risk of autism in a monotonically increasing fashion (Table 2, Model 1). The 1,125 women exposed to the highest level of combined physical, emotional and sexual abuse in childhood were at greatest risk of having a child with autism compared with women unexposed to childhood abuse (risk ratio = 3.7, 95% confidence interval = 2.3, 5.8, $P<0.001$).

In the model including perinatal risk factors, childhood abuse remained highly significantly associated with increased risk for autism, although risk ratio estimates were slightly attenuated (Table 2, Model 2). The perinatal factors we examined statistically accounted for 7% of the association between child abuse and autism risk, although this estimate did not

statistically differ from zero. Models stratified by sex showed similarly elevated risk of autism in female and male children of women exposed to childhood abuse, and an abuse-by-sex interaction term was not statistically significant. As only 125 women were exposed to SSRIs in the perinatal period, models including SSRI use would not converge. We therefore excluded SSRI use as a potential mediator.

We conducted further analyses to identify which of the perinatal factors were most important in mediating the association between childhood abuse and risk of autism in offspring. We calculated mediation for each perinatal factor separately, adjusted for maternal childhood SES and age at birth, and the birth year and sex of the child. In these analyses, we found gestational diabetes (mediation=3.5%) and abortion prior to the birth (mediation=3%) to be the strongest mediators of the child abuse/autism relationship. Smoking during pregnancy mediated 2% of the association, and the remaining variables mediated 1% or less.

As childhood abuse was strongly associated with most of the perinatal factors examined, we conducted additional analyses to investigate whether child abuse might explain the statistical relationship between the perinatal factors and autism, in other words, whether childhood abuse might confound the association between these factors and autism. We examined the association of autism with each perinatal factor in separate models, adjusted for demographic factors, with and without childhood abuse as an additional independent variable.

In these analyses, the associations between autism and prior abortion, smoking, and intimate partner violence were somewhat attenuated after adjustment for childhood abuse (attenuation range, 12 to 19%). The association of gestational diabetes and autism was very slightly attenuated. The associations of pregnancy <37 weeks and low birth weight with autism were not attenuated after adjusting for childhood abuse. Preeclampsia and alcohol use were not associated with autism.

Discussion

We found maternal exposure to abuse in childhood was associated with elevated risk of autism in a monotonically increasing fashion. Notably, women exposed to the highest level of physical/emotional abuse, comprising one-quarter of the women in our study, were at 60% elevated risk of having a child with autism compared with women not exposed to abuse. Additionally, we found that an array of perinatal factors were associated with both child abuse history and autism risk. However, these factors accounted for only a small part of the relationship between maternal abuse history and autism. No prior studies have examined early-life maternal exposures to stressors as possible risk factors for autism, however, several maternal stressors in the prenatal period have been associated with risk of autism, such as stressful life events[9,35,36], though findings are mixed[37].

Our results are consistent with at least four possibilities. First, additional unmeasured perinatal adverse circumstances associated with childhood abuse, such as infection[38–40],

poor diet[41], insufficient prenatal care[2], medication use[8], illegal drug use[11], and stressful life events[17,42,43], may account for all of the association we found.

Second, the experience of childhood abuse and its behavioral, psychological and physical sequelae may cause alterations to the mother's biological systems, including the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-pituitary-gonadal (HPG) axis, and the immune system, which may in turn directly increase risk of autism in children. Childhood abuse has been associated with dysregulated HPA axes in both women[44–46] and their infants[47]. Dysregulation of the HPA axis has been observed in persons with autism[48], and it has been hypothesized that dysregulation of the maternal HPA axis affects the fetal brain[49,50]. Additionally, exposure to acute psychosocial stressors may increase secretion of androgen[51,52], and some evidence suggests that exposure to high prenatal concentrations of androgen is associated with autistic traits.[53,54] However, whether childhood abuse leads to persistently elevated maternal androgens is unknown. Immune dysfunction has also been associated with exposure to childhood abuse[55–60]. Immune dysfunction and inflammation, including neuroinflammation, are more prevalent in persons with autism[61–66]. Maternal inflammation affects the developing brain and maternal inflammation and immune function[67–69] have been hypothesized to be causes of autism[70–74].

Third, mother's exposure to childhood abuse may, through epigenetic[75,76] or other mechanisms, increase her biological reactivity to physical and psychological stressors through sensitization of the central nervous system[45], dysregulation of the HPA axis[77], and effects on the prefrontal cortex that impact the threat-appraisal response system[78]. Hyperreactivity to stressors may in turn negatively affect the developing fetus through effects on the mother and fetus' HPA and HPG axes and immune system function[79].

Fourth, mother's exposure to abuse in childhood may be an indicator of genetic risk for autism, as mental illness in parents is associated with child abuse perpetration[80–82], and several studies have suggested that genetic risk for autism may overlap with genetic risk for other mental disorders[7,83–86]. Thus, perpetration of child abuse by the grandparents and experience of abuse in childhood by the mother may be indicators of genetic risk for autism in the child.

Our study identifies an intergenerational association between a woman's childhood exposure to violence and risk for a severe developmental disorder in her children. Given the numerous sequelae of the adverse perinatal circumstances we examined[87–92], it is likely that children of women exposed to childhood abuse suffer from higher prevalence of a constellation of additional health problems compared with children of women who were not abused. Prior studies of the association between childhood abuse and perinatal risk factors have generally been conducted in small samples with a limited range of outcomes examined.[93,94] Thus, the present study is the most comprehensive examination to date of the relationship between maternal childhood abuse and perinatal risk factors in a large population-based sample.

Our results should be considered in light of two important limitations. First, child's autism, participant's childhood abuse and participants' gestational exposures were by participant report. Report of autism was validated by the ADI-R, an instrument with good reliability and

validity[24,95]. While this approach is consistent with a large body of epidemiologic research, it does not constitute a diagnosis. Self-report of health-related circumstances in this cohort of professional nurses has been highly accurate in multiple validation studies.[96–98] Nonetheless, misreporting of autism, childhood abuse exposure, or gestational exposures may have biased our results. Second, women reported their exposure to childhood abuse after knowing that they had a child with autism. If knowledge of their child's autism status affected their report of experience of childhood abuse, this may have biased our results. However, women's experience of childhood abuse was not queried in the context of her children's autism status. Childhood abuse and autism were assessed in separate questionnaires four years apart, thus reducing likelihood of bias.

If the association we identify here between maternal childhood abuse and autism is due in part to direct or indirect effects of abuse (as opposed to shared genetic risk for abuse exposure and autism), this has several implications for clinical practice. First, we provide another compelling reason to increase efforts to prevent childhood abuse. Second, we identify a population at elevated risk of having a child with autism, women with a history of moderate or serious childhood abuse. Third, given the suggestion of mediation of autism risk through adverse perinatal circumstances, we suggest a possible means of reducing autism risk in children of these women, namely, though prevention of adverse perinatal circumstances.

In terms of research, studies examining perinatal risk factors for autism should consider potential confounding by maternal childhood abuse. Maternal abuse was strongly associated with nearly every perinatal risk factor we examined, and adjustment for abuse attenuated the associations of several perinatal risk factors with autism. If maternal abuse increases risk of autism through mechanisms not mediated by perinatal risk factors, or if maternal abuse is an indicator of genetic risk for autism, studies examining perinatal risk factors may find statistical associations with autism even if the factors play no causal role in autism etiology. If childhood abuse is associated with autism primarily through shared genetics, mental disorders that specifically increase risk for child abuse perpetration may overlap genetically with those that increase risk for autism. Future work should further investigate causal mechanisms by which maternal child abuse may be associated with autism.

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Abbreviations

RR	Risk ratio
CI	confidence interval
ADI-R	Autism Diagnostic Interview- Revised

PDD-NOS	pervasive developmental disorder – not otherwise specified
HPA axis	hypothalamic-pituitary-adrenal axis
HPG axis	hypothalamic-pituitary-gonadal axis

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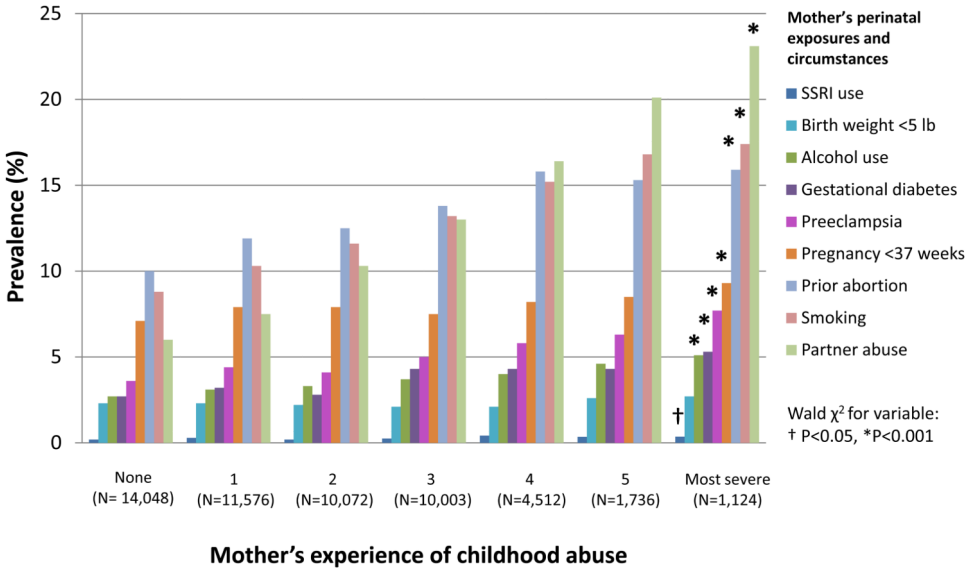

Figure.

Perinatal adverse circumstances by mother's exposure to childhood physical, emotional and sexual abuse, Nurses' Health Study II (n=52,949)

Table 1

Mother's exposure to childhood sexual or physical and emotional abuse and risk of autism in her child, Nurses' Health Study II (N autism cases = 451, N controls = 52,498)[†]

		Model 1	Model 2
	N	Risk ratio (95% confidence interval)	
Childhood sexual abuse			
None	35,175	1.0 [Reference]	
Mild	12,595	1.2 (1.0. 1.5)	
Moderate	3,391	1.2 (0.8, 1.7)	
Severe	1,788	2.0 (1.3, 3.1)**	
Childhood physical and emotional abuse			
None	18,342		1.0 [Reference]
2nd quartile	11,516		1.0 (0.8, 1.4)
3rd quartile	10,545		1.2 (0.9, 1.5)
Top quartile	12,546		1.6 (1.3, 2.1)***

[†]Models are adjusted for mother's age at birth, year of birth of the child, mother's socioeconomic status in childhood, and sex of child.

Wald χ^2 significant: ** P<0.01, *** P<0.001.

Table 2

Mother's exposure to combined sexual, physical, and emotional childhood abuse and risk of autism in her child, with and without perinatal risk factors, Nurses' Health Study II, (N autism cases = 447; N controls = 52,478)[†]

		Model 1: Unadjusted for perinatal factors	Model 2: Adjusted for perinatal factors
	N	Risk ratio (95% confidence interval)	
Childhood physical, emotional, and sexual abuse			
0: None	14,008	1.0 [Reference]	1.0 [Reference]
1	11,551	1.1 (0.9, 1.5)	1.1 (0.8, 1.4)
2	10,045	1.2 (0.9, 1.6)	1.1 (0.9, 1.5)
3	9,969	1.5 (1.2, 2.0)	1.4 (1.0, 1.8)
4	4,497	1.6 (1.1, 2.3)	1.3 (0.9, 1.9)
5	1,731	1.7 (1.0, 2.9)	1.4 (0.9, 2.4)
6: Most severe	1,124	3.7 (2.3, 5.8)***	3.0 (1.9, 4.8)***
Birth weight (pounds)			
Less than 5			2.2 (1.2, 3.7)
5 to 5.4			1.3 (0.6, 2.9)
5.5 to 6.9			1.2 (1.0, 1.6)
7 to 8.4			1.0 [Reference]
8.5 to 9.9			1.1 (0.9, 1.4)
10 or more			1.3 (0.8, 2.2)
Gestational diabetes			1.8 (1.3, 2.5)***
Smoking during pregnancy			1.3 (1.0, 1.8)
Abortion prior to birth			1.3 (1.0, 1.6)
Alcohol during pregnancy			
None	45,745		1.0 [Reference]
1 drink/week	5,142		0.8 (0.6, 1.2)
2 or more drinks/week	1,745		0.9 (0.5, 1.6)
Preeclampsia			0.9 (0.6, 1.4)
Intimate partner abuse			1.4 (1.0, 1.8)*
Pregnancy length (weeks)			
Less than 37			1.1 (0.8, 1.6)
37 to 42			1.0 [Reference]
43 or more			0.9 (0.6, 1.3)

[†]Models are adjusted for mother's age at birth, year of birth of the child, mother's socioeconomic status in childhood, and sex of child.

Wald χ^2 for variable as a whole significant at: * P<0.05, ** P<0.01, ***P<0.001.